UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,174	03/10/2004	Gerhard Siemeister	SCH-1815-C1	3503

23599 7590 11/02/2006

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
HUGHES, ALICIA R	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/796,174	SIEMEISTER ET AL.	
	Examiner	Art Unit	
	Alicia R. Hughes	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8 and 12-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-11* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-7 and 9-11 are currently pending and are the subject of this Office Action. Applicants cancelled claims 8 and 12-22 in the response filed on July 18, 2006.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-7 and 9-11, in the reply filed on July 18, 2006 is acknowledged. The Applicant's arguments have been considered and the Examiner maintains the restriction requirement, however is removing the election of species requirements for purpose of examining all pending claims.

Applicant's election with traverse of Group I, claims 1-7 and 9-11, in the reply filed on July 18, 2006 is acknowledged. The traversal is on the ground(s) that a search of all claims would comprise overlapping subject matter and therefore would not be an undue burden on the examiner to carry out a search. This is not found persuasive because that the claims in the instant application are very broad and do contemplate several distinct inventions, different compounds, for example, that are structurally and functionally different. As the examination of multiple inventions that would require an unduly burdensome search on the part of the examiner, restriction is proper.

The requirement is still deemed proper and is therefore made FINAL.

Objections

The applicant is reminded of the importance of proofreading in an effort to avoid misunderstanding of claims and information included in the specification by readers due to spelling and syntax errors. Claim 3 is objected to because the word "modulates" should be modulate to ensure proper subject-verb agreement. The specification is objected to, generally, for all errors and specifically, as it contains incorrect numbering that has been manually corrected and a misspelled word, "protocol," both on page 15, line 24.

Appropriate action is required.

The drawings are objected to, because figure 1 contains an improper legend and figures 2 and 3 are not legible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheets should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency.

Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the

drawings will not be held in abeyance. In addition to Replacement Sheets containing the corrected drawing figure(s), applicant is required to submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Sheets" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d)(1). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

Claim Rejections 35 U.S.C. §112.1

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-7 are drawn to pharmaceutical compositions comprising one or several agents as compound I and one or several agents as compound II. However, the specification only discloses art to support a single agent acting as compound I, and a single agent acting as

compound II. As a result, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim.

Claim Rejections – 35 U.S.C. §103(a)

The following is a quotation of 35 U.S.C. §103(a), which forms the basis for all obviousness rejections set forth in this office action:

> (a) A patent may not be obtained through the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 9-11 are rejected under 35 U.S.C. §103(a) as being obvious over Thorpe et al (U.S. Patent No. 6,703,020).

Claims 1, 4, and 6 of the instant invention are drawn, in part, to "[p]harmaceutical compositions ... comprising one or several agents as compound I which modulate the biological function of one or several of the VEGF/VEGF receptor systems." Claim 3 contains identical language, only differing from claims 1, 4, and 6, because the agent therein may "modulate[] the biological function of one or several of the VEGF/VEGF receptor systems *or* of one or several of the Angiopoietin/Tie receptor systems" (Emphasis added). Thorpe et al teach antibodies that have the ability to maintain VEGF binding to VEGFR1 (Col. 5, lines 29-31). Thorpe et al teach "the intention of using antibodies that do not substantially inhibit VEGF binding to VEGFR1 is to maintain biological functions mediated by VEGFR1" (Col. 5, lines 24-26). The reference further teaches that these antibodies "exhibit a reproducible ability to maintain VEGF binding to

VEGFR1 at levels of at least about 88%, about 90%, about 92%, about 95%, or of about 98-99% at any amount between about 100 fold molar excess of antibody over VEGF" (Col. 5, lines 31-35). The variation in the binding levels typifies a modulation in biological function.

Claims 2 and 5 of the instant invention are drawn, in part to "[p]harmaceutical compositions comprising one or several agents as compound I which are targeted to the endothelium via one or several of the VEGF/VEGF receptor systems." Claim 3 contains identical language to claims 2 and 5, only differing by omitting the phraseology "via one or several of the VEGF/VEGF receptor systems." Claim 6 contains identical language, only differing from claims 2 and 5, because the language is applied as compound II rather than compound I. Thorpe et al teach an antibody targeted to the endothelium via a VEGF/VEGF receptor system. More specifically, Thorpe et al teach "a VEGR2-blocking, anti-VEGF antibody may be identified by testing for the ability to inhibit VEGF-mediated endothelial cell growth (inhibiting the mitogenic activity of VEGF)" (Col. 6, lines 48-51). The reference further teaches that "[a]n antibody with an ability to inhibit VEGF-mediated endothelial cell growth will generally exhibit a consistently observed inhibition of VEGF-mediated endothelial cell growth of about 25%, 30%, 35%, 40%, 45%, or 50% or so" (Col. 6, lines 60-63).

Claims 1, 2, and 7 of the instant invention are drawn, in part, to "[p]harmaceutical compositions ... comprising one or several agents as compound II which modulate the biological function of one or several of the Angiopoietin/Tie receptor systems." Thorpe et al teach that angiopoietin-2 is a ligand for the Tie2 receptor that counteracts blood vessel maturation and stability mediated by angiopoietin-1, thereby acting to disturb capillary structure (Col. 81, lines 38-41). More specifically, Thorpe et al teach that angiopoietin-2 "imparts a negative signal to

the target cells and destabilization induced by angiopoietin-2 leads to vessel regression" (Col. 81, lines 42-44). Thorpe et al further teach that "an extreme biasing in the system in favor of regression, by perpetual angiopoietin-2 signaling, may well obliterate the effects of both angiopoietin-1 and VEGF" (Col. 81, lines 54-57).

Claims 4, 5, and 7 of the instant invention are drawn, in part, to "[p]harmaceutical compositions ... comprising one or several agents as compound II which are targeted to the endothelium via one or several of the Angiopoietin/Tie receptor systems." Thorpe et al teach that angiopoietin-1 is a receptor activator that acts through the Tie2 receptor, to promote the stabilization and the maintenance of mature vessels and it is thought to "convert immature vessels to []mature vessels by promoting interactions between endothelial cells and the surrounding support cells" (Col 80, lines 40-45). Thorpe et al also teach that angiopoietin-1 has a direct role "... on human endothelial cell and its interaction with other angiogenic molecules ... [work to] stabilize vascular structures by promoting the survival of differentiated endothelial cells" (Col. 80, lines 52-56).

Claim 9 of the instant application is drawn to pharmaceutical compositions according to claims 1-8 intended for simultaneous or separate sequential therapeutical application. Thorpe et al II teach antibodies that specifically inhibit VEGF binding to only one of the two VEGF receptors (Col. 1, lines 18-21), and that these antibodies may be used as part of a combination therapy (Col. 112, lines 14-15). More specifically, Thorpe et al II teach antibodies that "are used simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents, or targeted immunotoxins or coaguligands" (Col. 112, lines 27-34).

Claim 10 of the instant application is drawn to a pharmaceutical composition according to claims 1-8 which comprise as compound I at least ... "(d) compounds which inhibit or activate expression of a ligand or of a receptor of the VEGF or Tie receptor system." Thorpe et al II teach "that using a tumor-binding ligand to deliver angiopoietin-1 to tumor blood vessels would readily deliver on the order of 500,000 angiopoietin-1 molecules to a vessel lumen. This would overwhelm the Tie2 receptor system, totally saturating the Tie2 receptors with the angiopoietin-1 ligand" (Col. 80-81, lines 66-67 and 1-4, respectively). As a result of the Tie2 receptors being overly saturated, Angiopoietin-2 would be unable to bind and the combined result would be the inhibition of VEGF. (Thorpe et al II, Col 81, lines 4-6).

Claim 11 of the instant application is drawn to pharmaceutical compositions according to claims 1-8 which comprise as compound II at least ... "(l) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which are targeted to the endothelium and induce necrosis or apoptosis." Thorpe et al II teach components that induce necrosis in tumors in "combination with non-toxic substances or 'prodrugs.' The enzymes set free by necrotic processes cleave the non-toxic 'prodrug' into the toxic 'drug', which leads to tumor cell death" (Col. 113, lines 14-20).

In light of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to combine moieties of the VEGF/VEGF receptor system and Angiopoietin/Tie2 receptor system as disclosed by Thorpe et al., because both receptor systems when acting in combination, retain the ability to inhibit the vascularization of endothelial cells and prove effective aids in the treatment of cancer.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR of Public PAIR. Status information for unpublished applications is available through Public PAIR only. For information about the PAIR system, see http://pair-direct-uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

30 October 2006
ARH

Ardin H. Marschel 10/30/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER